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DINSMORE & SHOHL LLP
1900 CHEMED CENTER
255 EAST FIFTH STREET
CINCINNATI, OH 45202

EXAMINER	
ROONEY, NORA MAUREEN	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/651,136
Filing Date: August 28, 2003
Appellant(s): Sipka, Sandor
Bertok, Lorand
Bruckner, Geza
Ferenc, Schnitzer

Denise M. Everett
For Appellant

EXAMINER'S ANSWER

This is in response to the Appeal Brief filed 09/13/2010 appealing from the Office Action mailed 05/25/2010.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The Examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Cochran et al. 'Influence of lipopolysaccharide exposure on airway function and allergic responses in developing mice.' Pediatric Pulmonology 34:267-277, 2002.

Khan et al. 'Functional and immune response to lipopolysaccharide and allergens in developing mice.' Pediatric Research 51(4):474A, 2002.

Previte et al. 'Detoxification on Salmonella typhimurium lipopolysaccharide by ionizing radiation.' Journal of Bacteriology 93(5):1607-1614, 1967.

Baldridge et al. 'Monophosphoryl lipid A enhances mucosal and systemic immunity to vaccine antigens following intranasal administration.' Vaccine 18:2416-2425, 2000.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A. Claims 1-3, 5, 10, 13, 17-18 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cochran et al. in view of Previte et al. and Baldridge et al.

Cochran et al. teaches:

A process for decreasing development of allergic asthma (OVA induced asthma) comprising exposing an infant, neonatal or immature mammal maturing in an overly sterile environment shortly after birth (2-3 week old laboratory mice) to lipopolysaccharide derived from extracted bacterial endotoxin (E.coli LPS) by administering an aerosol spray composition of the mammal to a living environment/space (saline and air during nasal aspiration) during maturation of the mammal (at 2-3 weeks) (In particular, abstract, page 268, right column, whole document).

Cochran et al. also teaches that "recent studies raised the intriguing hypothesis that exposure to LPS may interact with the immune system in early life and produce a protective environment against the development of asthma and atopy. Despite the potential importance of

this phenomenon in the pathogenesis of childhood asthma, only recently have animal models been used to study the interactions between endotoxin and allergic responses as a function of age" and "patients become symptomatic in their first 5 years of life" (In particular, page 268, left column).

The claimed invention differs from the prior art by the recitations of:

"irradiation detoxified lipopolysaccharide" in claims 1-3, 5, 10, 13, 17-18, 22-25;

"wherein exposure comprises at least weekly administration during maturation of the mammal" of claim 1;

"wherein the irradiation-detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 kGy" in claim 2;

"wherein the irradiation changes the structure of the endotoxin while maintaining its Th1 stimulatory positive immune effect in the resulting irradiation-detoxified lipopolysaccharide" in claim 3;

"wherein the mammal is a human and during maturation is between 1 month and 2 years of age" of claim 13;

""during maturation" is throughout the maturing life cycle of the mammal" of claim 17;

"wherein administration is on a daily basis" of claim 18;

"wherein the mammal is a human infant and exposure comprises at least weekly administration from 1 month to 2 years of age" of claim 24 ; and

exposing a "human of up to about 2 years of age" and "wherein exposure comprises administration on an at least weekly basis of an aerosol spray composition comprising the irraditation-detoxified lipopolysaccharide at a concentration of 5-15 μg/ml" in claim 25.

Previte et al. teaches the detoxification of isolated LPS of S. typhimurium, S. enteritidis and E. coli using 4, 4.8 and 4.5 Mrad (about 25 to about 150 kGy) ionizing radiation. The detoxification eliminates lethality induced by its lethal determinants (changes the structure), while retaining antigenticity (maintaining its Th1 stimulatory effect) and pyrogenicity (In particular, abstract, whole document).

Baldridge et al. teaches the weekly intranasal vaccination of mice with the adjuvant monophosphoryl lipid A (MPL), which is derived from lipopolysaccharide and has retained immunostimulatory properties and decreased toxicity, resulting in increased Th1 responses (In particular, abstract, 'Vaccinations' section on page 2417, whole document).

The functional limitations of "operable to stimulate the Th1 arm of the human's immune system" of claims 1 and 22; and "operable to stimulate the Th1 arm of the human's immune system while reducing interleukin 1 (IL-1) stimulation caused by the native form of the lipopolysaccharide derived from extracted bacterial endotoxin" of claim 25; and "by restoring normal immune system development" in claim 22 are inherent properties of the reference irradiation-detoxified lipopolysaccharide. Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may be an inherent characteristic of the prior art, it has the authority to require the applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

It is noted that the specification does not provide a limiting definition for the terms "living environment" and "living space" Therefore, given their broadest reasonable interpretation, the terms apply to all things that are in a "living environment" or "living space" including saline and air.

Claims 1-3, 5, 10, 13, 17-19, 22-25 are included because it would be conventional and within the preview of those skilled in the art to identify and determine the optimal modes, doses and frequency of administration. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. It is also noted that the recitation of wherein the administration is on a daily

basis reads on a single administration without a further recitation regarding the number of days the administration occurs.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the process taught by Cochran et al in humans of 1 month to 2 years of age and during the maturing life cycle of the mammal. Cochran et al. suggests performing the process for decreasing development of allergic asthma in young children under 5 years of age implicitly.

One of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in the process for decreasing allergic asthma of Cochran et al. because the process should be safe and without toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Therefore, it is obvious to use a safer, less toxic form of LPS in neonatal or immature mammals to decrease allergic asthma.

It would have been obvious to administer the detoxified LPS at least weekly because Baldridge et al. teaches that the weekly intranasal administration of the detoxified LPS adjuvant monophosphoryl lipid A results in the generation of a Th1 response.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the

invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

B. Claims 1-3, 5, 10, 13, 17-18 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khan et al. in view of Previte et al. and Baldridge et al.

Khan et al. teaches:

A process for decreasing development of allergic asthma (OVA induced asthma) comprising exposing an infant, neonatal or immature mammal maturing in an overly sterile environment shortly after birth (3 week old laboratory mice) to lipopolysaccharide derived from extracted bacterial endotoxin (LPS) by administering an aerosol spray composition of the mammal to a living environment/space (saline and air during intratracheal aspiration) during maturation of the mammal (at 3 weeks) (In particular, abstract).

Khan et al. also teaches that "recent evidence has suggested that post-natal exposure to endotoxin may protect against the development of allergen sensitization and asthma"(In particular, abstract).

The claimed invention differs from the prior art by the recitations of:

"irradiation detoxified lipopolysaccharide" in claims 1-3, 5, 10, 13, 17-18, 22-25;

"wherein exposure comprises at least weekly administration during maturation of the mammal" of claim 1;

"wherein the irradiation-detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 kGy" in claim 2;

"wherein the irradiation changes the structure of the endotoxin while maintaining its Th1 stimulatory positive immune effect in the resulting irradiation-detoxified lipopolysaccharide" in claim 3;

"wherein the mammal is a human and during maturation is between 1 month and 2 years of age" of claim 13;

""during maturation" is throughout the maturing life cycle of the mammal" of claim 17;

"wherein administration is on a daily basis" of claim 18;

"wherein the mammal is a human infant and exposure comprises at least weekly administration from 1 month to 2 years of age" of claim 24; and

exposing a "human of up to about 2 years of age" and "wherein exposure comprises administration on an at least weekly basis of an aerosol spray composition comprising the irradiation-detoxified lipopolysaccharide at a concentration of 5-15 μg/ml" in claim 25.

Previte et al. teaches the detoxification of isolated LPS of S. typhimurium, S. enteritidis and E. coli using 4, 4.8 and 4.5 Mrad (about 25 to about 150 kGy) ionizing radiation. The detoxification eliminates lethality induced by its lethal determinants (changes the structure), while retaining antigenicity (maintaining its Th1 stimulatory effect) and pyrogenicity (In particular, abstract, whole document).

Baldridge et al. teaches the weekly intranasal vaccination of mice with the adjuvant monophosphoryl lipid A (MPL), which is derived from lipopolysaccharide and has retained immunostimulatory properties and decreased toxicity, resulting in increased Th1 responses (In particular, abstract, 'Vaccinations' section on page 2417, whole document).

The functional limitations "operable to stimulate the Th1 arm of the human's immune system" of claims 1 and 22; and "operable to stimulate the Th1 arm of the human's immune system while reducing interleukin 1 (IL-1) stimulation caused by the native form of the lipopolysaccharide derived from extracted bacterial endotoxin" of claim 25; and "by restoring normal immune system development" in claim 22 are inherent properties of the reference irradiation-detoxified lipopolysaccharide. Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter

may be an inherent characteristic of the prior art, it has the authority to require the applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

It is noted that the specification does not provide a limiting definition for the term "living environment" and "living space." Therefore, given their broadest reasonable interpretation, the terms apply to all things that are in a "living environment" or "living space" including saline and air.

Claims 1-3, 5, 10, 13, 17-19, 22-25 are included because it would be conventional and within the preview of those skilled in the art to identify and determine the optimal modes, doses and frequency of administration. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. It is also noted that the recitation of wherein the administration is on a daily basis reads on a single administration without a further recitation regarding the number of days the administration occurs.

Khan et al. teaches "recent evidence has suggested that post-natal exposure to endotoxin may protect against the development of allergen sensitization and asthma"(In particular, abstract), so it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the process taught by Khan et al in humans of 1 month to 2 years

of age and during maturation. Khan et al. suggests performing the process for decreasing development of allergic asthma in young post-natal children implicitly.

One of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in process for decreasing allergic asthma of Khan et al. because the process should be safe and without toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Therefore, it is obvious to use a safer, less toxic form of LPS in neonatal or immature mammals to decrease allergic asthma.

It would have been obvious to administer the detoxified LPS at least weekly because Baldridge et al. teaches that the weekly intranasal administration of the detoxified LPS adjuvant monophosphoryl lipid A results in the generation of a Th1 response.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

(10) Response to Argument

A. On pages 11-20 of the Appeal Brief, Appellant argues the following:

"The Examiner fails to establish a prima facie case for obviousness under 35 U.S.C. §103 because all claim limitations are not taught or suggested by the combination of Cochran, Previte and Baldridge and motivation to combine the references is absent.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981,180 USPQ 580 (CCPA 1974). Summarily, Appellants submit that the primary reference, Cochran, fails to teach or suggest at least three essential steps of the instant invention. First, as noted by the Examiner, Cochran used LPS rather than IR-LPS in his experiments. Second, Cochran teaches only a one-time exposure to an immature mammal, while Appellants claim repeated (at least weekly) exposure during the maturation period. Third, Cochran teaches administration of LPS directly inside the nostril of the subject (via intranasal instillation), while Appellants claim application of IR-LPS to the living environment of the mammal. The Examiner applies Previte ostensibly for the teaching of IR-LPS, although Previte teaches only administration by injection of IR-LPS to adult mammals to test for a decrease in toxicity, reporting death of nearly a third of the subjects 6 days post-administration (see, e.g., Fig. 3), and "extensive inactivation of antigenic components with increasing radiation dose" (page 1611, second column, line 11-14). The Examiner then applies Baldridge ostensibly for the teaching of at least weekly administration, although Baldridge makes no mention whatsoever of IR-LPS and is limited to methods of using monophosphoryl lipid A (MPL), a truncated derivative of LPS, as an adjuvant only in an antigen-containing vaccine. Baldridge does not teach the administration of MPL alone (or IR-LPS or LPS, for that matter), for any indication. And like Cochran, Baldridge teaches only the intranasal administration of MPL directly inside the nose of a subject, as part of an antigenic vaccine. The references, alone or in combination, fail to teach all elements of the claim. Namely, the combination of Cochran, Previte, and Baldridge fail to teach (1) administration of IR-LPS to an immature mammal, (2) at least weekly administration of IR-LPS, and (3) administration of IR-LPS to the living environment of the mammal.

With respect to the claim limitation of administering IR-LPS to a neonatal or immature mammal, Cochran teaches only the administration of LPS to immature mice. Previte teaches only the administration of IR-LPS to adult mice. Moreover, Previte discloses the retention of a degree of lethality upon direct administration to adult mammals that would certainly guide a practitioner away from direct administration to a more fragile immature subject. Indeed, Previte reports a death rate of 3/10 adult subjects 6 days post-administration. And yet, the Examiner expressly states the motivation for using Previte's IR-LPS in the method of Cochran is specifically because a practitioner would conclude, based on the teachings of Previte, that the method would be "safe" for children and infants. The Examiner's assertion that the motivation to combine the references is "because it would be safe for children" is untenable, given the reported death rate associated with Previte's findings. Appellants contend that a positive death rate of 3/10 adult subjects predictably due to the treatment, as disclosed by Previte for IR-LPS levels within the scope of the instant invention, would be universally understood as unacceptable and would guide a practitioner away from its use in neonatal or immature subjects. A person of ordinary skill in the art seeking methods to prophylactically decrease development of allergic asthma would be discouraged from employing the IR-LPS of Previte in the protocol of Cochran,

as Previte teaches a single relative high dose to adult rats which results in an unacceptably high death rate among the subjects.

Further, the Examiner fails to consider the distinguishing impact of the route and manner of administration. The Examiner cannot fairly conclude that the two methods are identical with respect to toxicity of the active, antigenicity of the active, or with respect to achieving the target outcome. Indeed, Appellants note that Previte supports this proposition, since Previte discloses a single dose of IR-LPS injected intraperitoneally to the subject, which results in toxicity to a relatively high percentage of subjects, whereas the instant inventive methods rely on repeated external dosing during the maturation period of the mammal by misting the environment without toxic effect. Clearly, given these disparate results, route and manner of administration are distinguishing factors that lead to different toxicity and antigenicity outcomes. Hence, Appellants submit the combination of Previte with Cochran is improper and fails to teach or suggest administering IR-LPS to a neonatal or immature mammal.

With respect to the claim limitation of at least weekly administration of IR-LPS, Cochran and Previte teach only a one-time dose of either LPS or IR-LPS to a subject. Baldridge teaches only the weekly delivery of a vaccine comprising an antigen and MPL, a truncated derivative of LPS, as an adjuvant. MPL differs structurally from LPS. Nevertheless, the Examiner asserts it would have been obvious to administer IR-LPS "at least weekly" in the method of Cochran because "Baldridge teaches that the weekly intranasal administration of the detoxified LPS adjuvant monophosphoryl lipid A results in the generation of a Th 1 response." However, this application of Baldridge ignores the fact that (1) MPL differs structurally from LPS and IR-LPS, and (2) the MPL of Baldridge was never administered alone to a subject, nor was administration of MPL alone suggested by Baldridge for any indication. Rather, the MPL of Baldridge was merely administered as an adjuvant in a vaccine.

Given these substantial differences between the methods, Appellants submit the application of Baldridge for the limitation of weekly administration of IR-LPS amounts to nothing more than improper hindsight reasoning. When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 USPQ 929, 933 & n.14 (Fed. Cir. 1984). "Hindsight" reconstruction is engaged in when an implication is made that a word or element describes the "differences," an element describable by that word is picked from a prior reference, the asserted prior art reference is focused on for that isolated teaching while disregarding, inter alia, how the disclosed element works, and making no finding of a suggestion that items found separately in prior references could or should be combined as in the claim at issue. See Panduit Corp. v. Dennison Manufacturing Co., 1 USPQ.2d 1593, 1602 (Fed. Cir. 1987). Appellants submit that this is precisely what the Examiner has done in this instance: the Examiner has relied on Baldridge for the isolated teaching of weekly administration, disregarding the differences of both structure of the active ingredient (MPL vs. IR-LPS) and method of administration (alone vs. as an adjuvant in a vaccine). There is simply no explanation for the Examiner's selection of "weekly administration" from Baldridge, other than hindsight gleaned from the instant invention.

Hence, Appellants submit the combination of Cochran, Previte, and Baldridge is improper and fails to teach or suggest at least weekly administration of IR-LPS.

With respect to the limitation of administration of IR-LPS to the living environment of the mammal, all of the cited references teach either the direct intranasal administration inside the naris of a subject (Cochran/Baldridge) or direct intraperitoneal injection (Previte).

Absent a definition provided in the specification, a claim term is afforded its common definition in the art. Appellants submit the common definition of the term "to a living environment of the mammal," is understood to refer to the environment external to the mammal -- that is, the mammal's external living surroundings. Clearly, direct intraperitoneal injection does not constitute administration to the living environment of the mammal. Similarly, the intranasal administration taught by Cochran and Baldridge is accomplished by restraining an animal and instilling a solution directly inside the naris of the animal. Appellants submit this invasive mode of administration is not the same as, nor encompassed by the term "application to the living environment of the mammal." In fact, none of the applied references teach or suggest the administration of IR-LPS to the external surroundings, or living environment, of the mammal. In every instance, the animals treated by Cochran, Previte, and Baldridge were restrained and/or sedated so that a solution could be placed directly inside the nose of the animal or injected directly into the peritoneal cavity. Hence, Appellants submit the combination of Cochran, Previte, and Baldridge fails to teach or suggest the limitation "to a living environment of the mammal."

All claim limitations must be considered in an obviousness rejection. 35 U.S.C §103 provides that:

> A patent may not be obtained.., if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

(Emphasis added). Since Cochran, Previte, and Baldridge together fail to address all claim limitations, Appellants assert the combined references fail to render obvious the subject matter as a whole. Absent any teaching or suggestion of the missing claim elements, Appellants submit the Examiner has failed to establish a prima facie case of obviousness under 35 U.S.C. § 103.

"Cochran, Previte and Baldridge do not enable the instant inventive methods since the combination of references does not place the claimed invention in the possession of the public.

To render a later invention unpatentable for obviousness, the prior art must enable a person of ordinary skill in the art to make and use the later invention. The prior art must place the claimed invention in the possession of the public. Beckman Instruments, Inc. v. LKB Produktor LB, 892 F.2d 1547, 1551 (Fed. Cir. 1989). Appellants submit the combination of Cochran, Previte and Baldridge does not enable the instant invention, since all claim elements are not taught or suggested by the references and one of ordinary skill in the art could not derive the

claimed methods from the cited references without undue experimentation.

Even if the combination of Cochran, Previte and Baldridge were proper (which Appellants contend it is not, in detail above), the combination itself still fails to enable the instant inventive methods, Combining the IR-LPS of Previte with the protocol of Cochran and the weekly administration of Baldridge still enables, at best, nothing more than invasive, intranasal instillation or injection of a solution comprising IR-LPS. Appellants note that the ultimate findings of Cochran teach only that a "single airway exposure to LPS in young mice leads to airway hyperresponsiveness." (Cochran, p. 272, col. 1, lines 6-8). Appellants' methods, however, require external administration of IR-LPS to the living environment of the mammal through repeated treatments during the maturation of the mammal.

Deriving the instant methods from a reading of Cochran, Previte and Baldridge requires altering the mode of administration, which would require undue experimentation on the part of the ordinary skilled artisan to achieve. That is, a practitioner would need to first conceive of the idea of administering IR-LPS to the external living environment of the mammal, rather than internal intranasal instillation (Cochran/Baldridge) or injection (Previte) of the mammal itself, without any guidance or direction whatsoever in the cited references. Then, the practitioner would need to experiment with different dosing regimens - varying from the single doses described in both Cochran and Previte - in order to determine the present inventive method of decreasing development of allergic asthma in the mammal. Given the unpredictability in the art, the absence of direction in Cochran, Previte and Baldridge, and the quantity of experimentation needed relative to the references, Appellants contend such a leap would necessarily require undue experimentation on the part of the ordinary skilled artisan.

Since Cochran, Previte and Baldridge together fail to place the present invention in the possession of the public, Appellants submit the instant inventive methods are not enabled by Cochran, Previte and Baldridge."

"Secondary evidence of nonobviousness rebuts any prima facie case and demonstrates the unexpectedly superior results of IR-LPS relative to LPS in the methods of the instant invention."

Even if a prima facie case of obviousness under §103 were established, Appellants' secondary evidence of nonobviousness rebuts the case. The Declaration of Dr. Sandor Sipka, M.D., Ph.D., executed February 23, 2009, filed March 2, 2009 ("The March 2009 Declaration"), included herewith in the Evidence Appendix, demonstrates unexpected results and must be afforded due consideration."

i.) The evidence should be afforded substantial weight because a nexus exists between the claimed invention and the evidence of unexpected results provided in the March 2009 Declaration.

In the March 2009 Declaration, Dr. Sipka described protocols and results relating to comparing the in vivo immunomodulatory effects of IR-LPS versus LPS when administered in accordance with the instant invention (as a mist sprayed externally into the environment). As stated by Dr. Sipka, the results clearly demonstrate that "prolonged pretreatment of the environment of infant mice with IR-LPS acts to prevent the intensity of ragweed specific allergic reaction differentially when compared to native LPS" (page 3, paragraph 6).

The Examiner has asserted that the Declaration does not provide evidence of an unpredicted differential impact of IR-LPS over LPS. The Examiner merely dismissed the data set forth in the Declaration as "neither surprising nor ... commensurate in scope with the claims, which are directed to a method of decreasing development of allergic asthma in neonatal or immature mammals by administration to a living environment of the mammal at least weekly."

To be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the subject matter as claimed. The examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281,305, 227 USPQ 657, 673-674 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). The term "nexus" designates a factually and legally sufficient connection between the objective evidence of nonobviousness and the claimed invention so that the evidence is of probative value in the determination of nonobviousness. Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 7 U.S.P.Q.2d 1222 (Fed. Cir.), cert. denied, 488 U.S. 956 (1988).

Appellants submit the March 2009 Declaration is most certainly relevant to the instantly claimed methods. The experimental method reported in the March 2009 Declaration aligns with the present claims, including (1) exposing immature mammals (6 week mice at beginning of treatment) to either IR-LPS or LPS (2) on an at least weekly basis (daily for eight weeks, during the maturation period of the mammal) (3) to the living environment of the mammal (misting the cages). In order to assess the effects on development of allergic disease, animals were then sensitized with ragweed allergen and later challenged with the allergen. Macrophage and neutrophil counts were determined for bronchial lavage samples (BAL), as well as cytokine concentrations for TNF-α (a TH 1 cytokine), IL-4, and IL-5 (a Th 2 cytokine). (See March 2009 Declaration, page 2, paragraph 4). The effect on allergic disease development was evaluated by assessing these indicators of allergic disease -- macrophage and neutrophil numbers, as well as in vivo immunomodulatory effects on cytokines, particularly the TH 1 cytokine, TNF-α.

Clearly, a nexus exists between the claimed invention, which provides methods for decreasing allergic asthma, and the data, which demonstrate the comparative unexpected superiority of IR-LPS in protecting against allergic disease, as evidenced by analysis of macrophage and neutrophil numbers as well as TNF-α levels. That is, a legally and factually sufficient connection between the claimed invention and the objective evidence of nonobviousness is present, such that the evidence should be considered in the determination of nonobviousness. Given the nexus between Dr. Sipka's data and the instant claimed invention,

Appellants submit the Examiner erred in failing to consider and afford proper weight to the factual evidence provided by Dr. Sipka in the March 2009 Declaration.

ii.) The surprisingly superior effect of IR-LPS over native LPS provides evidence of unexpected results that rebuts any prima facie ease of obviousness.

Appellants submit the results reported in the March 2009 Declaration provide evidence of the surprising superiority of IR-LPS compared to native LPS, with respect to stimulating the TH 1 arm of the immune system and protecting against hyper-immune response to an allergen. According to Dr. Sipka, the results illustrate "a striking difference between the in vivo immunomodulatory effects of IR-LPS and native LPS on macrophage and neutrophil numbers," (March 2009 Declaration, page 3, paragraph 6). Further, TNF-α levels were increased significantly by 3.56 fold compared to controls for the IR-LPS, as compared with 1.66 fold for native LPS (see March 2009 Declaration, page 3, paragraph 6). Dr. Sipka specifically stated the results indicate a "surprisingly superior effect of IR-LPS over LPS in protecting against the development of hyper-immune response to an allergen neither taught nor suggested by any of the prior art" cited by the Examiner or known to him (March 2009 Declaration, page 4, paragraph 7).

Neither Cochran, Previte nor Baldridge teach or suggest the superior effects of IR-LPS compared to native LPS in protecting against the development of allergic disease. Accordingly, Appellants submit the March 2009 Declaration provided by Dr. Sipka constitutes secondary evidence of nonobviousness rebutting any prima facie case of obviousness, since it clearly demonstrates that, specifically with respect to the methods of the instant invention, IR-LPS yields unexpectedly superior results in decreasing allergic response, relative to native LPS.

For the reasons set forth above, Appellants respectfully request that the Board reverse the final rejection of claims 1-3, 5, 10, 17-18, and 22-25 as being obvious under 35 U.S.C. §103 over Cochran in view of Previte and Baldridge."

Appellant's arguments have been fully considered, but are not found persuasive.

It is the Examiner's position that one of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in the process for decreasing allergic asthma of Cochran et al. because the process should be safe and without toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity.

Therefore, it is obvious to use a safer, less toxic form of LPS in neonatal or immature mammals to decrease allergic asthma. Baldridge et al. teaches that at least weekly administration of LPS-derived MPL results in a protective Th1 response, so it would be obvious to perform the method of Cochran and Previte at least weekly to attain a protective Th1 response to decrease allergic asthma.

Applicant's assertion that the common definition of the term "to a living environment of the mammal," is understood to refer to the "environment external to the mammal" or "the mammal's external living surroundings" is not supported by facts. The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01 In addition, even as defined above by Applicant, saline and air are both encompassed by these definitions. Saline and air are external to the mammal and in their living environment prior to administration intraperitoneally and intranasally. Applicant's argument about the invasiveness and restraint of the method of administration playing a role in whether or not application is from a living environment is not persuasive. Applicant intends for this invention to encompass diapers and wipes, which undeniably involve restraint and invasiveness in their application.

The dosing schedule is an art-recognized results-effective variable which is well within the purview of those of ordinary skill in the art at the time the invention was made. Therefore, the recited at least weekly dosing schedule lends no patentable import to the claimed invention. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller,

220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). See MPEP § 2144.05 part II. Applicants have not provided evidence of the criticality of the claimed dosing schedule, nor have they shown that the claimed dosing schedule produces unexpected results. The Examiner has additionally provided the Baldridge et al. reference to make the record clear that one of ordinary skill in the art would administer LPS-derived compounds at least weekly and that the resulting immune response would be the Th1 response that is necessary to establish a protective effect in the treatment of allergic asthma.

Applicant's arguments that the MPL of Baldridge et al. and LPS differ in structure and that MPL was only given in Baldridge et al. as an adjuvant are unpersuasive. The effect of the LPS and LPS derived MPL molecule is the same: to drive a Th1 response in the presence of other antigens to skew the response that is generated to the antigen. Therefore, the instant method and Baldridge references are directed to the same mechanism of action. Baldridge demonstrates that more than once weekly administration of LPS-derived MPL induces a Th1 response, as expected.

Applicant's argument that the Previte reference teaches away from the claimed invention is unpersuasive. It is the Examiner's position that Previte teaches that lethality is decreased in general and that is all that is required of the reference to make the argument that when giving LPS to children irradiated LPS would be preferred since it exhibits decreased lethality over non-irradiated LPS. Applicant's assertions that lethality is still higher than what would be considered acceptable in a treatment and that Previte teaches an unacceptable degree of toxicity for medical uses is unpersuasive. For purposes of the instant rejection what is or is not an acceptable degree of toxicity is not for Applicant to decide, nor is it a matter of what standards are presently

medically acceptable for humans in the United States. The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01 The reference teaches that toxicity is decreased and that teaching alone provides motivation to use irradiated LPS in place of LPS. It is noted that LPS is fully toxic and is being used medically in both the Previte et al. and Cochran et al. references.

The facts that Previte administers IR-LPS intraperitoneally to adult subjects and not to neonates and does not teach the use of IR-LPS to treat asthma does not preclude the use of the reference in the instant rejection. The Previte reference is relied on for its teaching that irradiated LPS is less toxic than non-irradiated LPS.

It is the Examiner's position that if the instant claims are enabled, so is the prior art. If irradiated LPS stimulates the Th1 arm of the animal's immune system in accordance with the present methods, then it would function in the same manner in the prior art. The motivation to use irradiated LPS over LPS has to do with decreased toxicity. The stimulation of the Th1 arm of the animal's immune system is inherent in using the irradiated LPS. Therefore, it remains the Examiner's position that the combination of the references does indeed place the claimed invention in possession of the public.

A showing of unexpected results must be based on evidence, not argument or speculation. In re Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997) (conclusory statements that claimed compound possesses unusually low immune response or unexpected biological activity that is unsupported by comparative data held insufficient to overcome prima facie case of obviousness). The declaration by Sandor Sipka filed on

03/02/2009 provides evidence of the effect of irradiated vs. non-irradiated LPS given daily in aerosol form for 8 weeks on the development of macrophages and neutrophils in bronchial lavage and the production of TNF-α and IL-5 in serum of young mice sensitized peritoneally with ragweed antigen after challenge with ragweed antigen (presumably also peritoneally, but the declaration is silent as to the route of challenge administration). It is noted that models of allergic asthma generally use a respiratory challenge, not a peritoneal challenge.

The results set forth in the 03/02/2009 declaration by Sandor Sipka do not provide evidence of decreased development of allergic asthma. It is argument and speculation to say that that measuring macrophages, neutrophils, TNF-α and IL-5 in the mice is evidence of unexpectedly decreased development of allergic asthma. Allergic asthma is characterized by airway hyperresponsiveness, eosinophilic lung inflammation, mucus hypersecretion and elevated IgE. Applicants have not met their burden of establishing that allergic asthma was decreased at all in the IR-LPS treated animals, much less decreased unexpectedly.

The results set forth in the declaration, specifically Tables I and II are not surprising or unexpected. First, there is no evidence of record indicating that a protective effect is generated by decreased macrophages and neutrophils, as there is no evidence to suggest that increased macrophages and neutrophils are associated with allergic asthma. Further, p values of .04 and .02, respectively are not evidence of surprising results. Further, there is no evidence of record to show that increased TNF-α and IL-5 are associated with a protective effect. The significant difference in TNF-α with a p value of .0001 is not evidence of a surprising result because there is no establishment on the record the increased TNF-α is independently protective against the development of allergic asthma. In the same way, the data showing that IL-5 is undetectable in

LPS and control, but detectable in IR-LPS does not establish surprising results. The data taken together shows that irradiated LPS is not surprisingly better than non-irradiated LPS, even in the specific variables measured. It is noted that LPS has been shown in the literature to provide a protective effect, so the data should demonstrate that already established protective effect as well as the surprisingly protective effect of IR-LPS over LPS. It is noted that evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991.

Even if Applicants had met their burden to establish unexpected results, the results are not commensurate in scope with the claims. The results do not demonstrate decreased development of allergic asthma in a neonatal or immature mammal by exposure with irradiation-detoxified LPS to a living environment. The claims encompass: 1.) asthma induced by any allergen, including allergens completely different from ragweed or pollen, such as cat and dust mite allergens; 2.) decreasing allergic asthma in all mammals, including humans; and 3.) exposing the mammal to IR-LPS by way of anything in their living environment. It remains the Examiner's position that the Declaration of Sandor Sipka is not sufficient to establish unexpected

results for the exact experiments set forth in the declaration, much less for the full scope of the claims.

B. On pages 25-20 of the Appeal Brief, Appellant argues the following:

The Examiner fails to establish a prima facie ease for obviousness under 35 U.S.C. §103 because all claim limitations are not taught or suggested by the combination of Khan, Previte, and Baldridge and motivation to combine the references is absent.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981,180 USPQ 580 (CCPA 1974). Summarily, Appellants submit that Khan fails to teach or suggest at least three essential steps of the instant invention. First, as noted by the Examiner, Khan used LPS rather than IR-LPS in his experiments. Second, Khan teaches only a one-time exposure to an immature mammal, while Appellants teach repeated exposure over the maturation period. Third, Khan teaches application of LPS invasively to the subject (via intratracheal administration), while Appellants teach exposure by application of IR-LPS to the external living environment of the mammal. The Examiner applies Previte ostensibly for the teaching of IR-LPS, although Previte teaches• only administration by injection of IR-LPS to adult mammals to test for a decrease in toxicity; reporting death of nearly a third of the subjects 6 days post-administration (see, e.g., Fig. 3), and "extensive inactivation of antigenic components with increasing radiation dose" (page 1611, second column, line 11-14). The Examiner then applies Baldridge ostensibly for the teaching of at least weekly administration, although Baldridge makes no mention whatsoever of IR-LPS and is limited to methods of using monophosphoryl lipid A (MPL), a truncated derivative of LPS, as an adjuvant only in an antigen-containing vaccine. Baldridge does not teach the administration of MPL alone (or IR-LPS or LPS, for that matter), for any indication. Baldridge teaches only the intranasal administration of MPL directly inside the nose of a subject, as part of an antigenic vaccine. The references, alone or in combination, fail to teach all elements of the claim. Namely, the combination of Khan, Previte, and Baldridge fail to teach (1) administration of IR-LPS to an immature mammal, (2) at least weekly administration of IR-LPS, and (3) administration of IR-LPS to the living environment of the mammal.

With respect to claim limitation of administering IR-LPS to a neonatal or immature mammal, Khan teaches only the administration of LPS to immature mice. Previte teaches only the administration of IR-LPS to adult mice. Moreover, Previte discloses the retention of a degree of lethality upon direct administration to adult mammals that would certainly guide a practitioner from direct administration to a more fragile immature subject. Previte reports a death rate of 3/10 adult subjects 6 days post-administration. And yet, the Examiner expressly states the motivation for using Previte's IR-LPS in the method of Khan is specifically because a practitioner would conclude, based on the teachings of Previte, that the method would be "safe" for children and infants. The Examiner's assertion that the motivation to combine the references

is "because it would be safe for children" is untenable, given the reported death rate associated with Previte's findings. Appellants contend that a positive death rate of 3/10 adult subjects predictably due to the treatment, as disclosed by Previte for IR-LPS levels within the scope of the instant invention, would be universally understood as unacceptable and would guide a practitioner away from its use in neonatal or immature subjects. A person of ordinary skill in the art seeking methods to prophylactically decrease development of allergic asthma would be discouraged from employing the IR-LPS of Previte into the protocol of Khan, as Previte teaches a single relative high dose to adult rats which results in an unacceptably high death rate.

Further, the Examiner fails to consider the distinguishing impact of the route and manner of administration. The Examiner cannot fairly conclude that the two methods are identical with respect to toxicity of the active, antigenicity of the active, or with respect to achieving the target outcome. Indeed, Appellants note that Previte supports this proposition, since Previte discloses a single dose of IR-LPS injected intraperitoneally to the subject, which results in toxicity to a relatively high percentage of subjects, whereas the instant inventive methods rely on repeated external dosing during the maturation period of the mammal by misting the environment without toxic effect. Clearly, given these disparate results, route and manner of administration are distinguishing factors that lead to different toxicity and antigenicity outcomes. Hence, Appellants submit the combination of Previte with Khan is improper and fails to teach or suggest administering IR-LPS to a neonatal or immature mammal.

With respect to claim limitation of at least weekly administration of IR-LPS, Khan and Previte teach only a one-time dose of either LPS or IR-LPS to a subject. Baldridge teaches only the weekly delivery of a vaccine comprising an antigen and MPL, a truncated derivative of LPS, as an adjuvant. MPL differs structurally from LPS:

Nevertheless, the Examiner asserts it would have been obvious to administer IR-LPS "at least weekly" in the method of Khan because "Baldridge teaches that the weekly intranasal administration of the detoxified LPS adjuvant monophosphoryl lipid A results in the generation of a Th 1 response." However, this application of Baldridge ignores the fact that (1) MPL differs structurally from LPS and IR-LPS, and (2) the MPL of Baldridge was never administered alone to a subject, nor was administration of MPL alone suggested by Baldridge for any indication. Rather, the MPL of Baldridge was merely administered as an adjuvant in a vaccine.

Given these substantial differences between the methods, Appellants submit the application of Baldridge for the limitation of weekly administration of IR-LPS amounts to nothing more than improper hindsight reasoning. When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 USPQ 929, 933 & n.14 (Fed. Cir. 1984). "Hindsight" reconstruction is engaged in when an implication is made that a word or element describes the "differences," an element describable by that word is picked from a prior reference, the asserted prior art reference is focused on for that isolated teaching while disregarding, inter alia, how the disclosed element works, and making no finding of a suggestion that items found separately in prior references could or should be combined as in the claim at issue. See Panduit Corp. v.

Dennison Manufacturing Co., 1 USPQ.2d 1593, 1602 (Fed. Cir. 1987). Appellants submit that this is precisely what the Examiner has done in this instance: the Examiner has relied on Baldridge for the isolated teaching of weekly administration, disregarding the differences of both structure of the active ingredient (MPL vs. IR-LPS) and method of administration (alone vs. as an adjuvant in a vaccine). There is simply no explanation for the Examiner's selection of "weekly administration" from Baldridge, other than hindsight gleaned from the instant invention. Hence, Appellants submit the combination of Khan, Previte, and Baldridge is improper and fails to teach or suggest at least weekly administration of IR-LPS.

With respect to the limitation of administration of IR-LPS to the living environment of the mammal, all of the cited references teach only invasive administration to a subject: intratracheal (Khan), intranasal (Baldridge), or intraperitoneal injection (Previte).

Absent a definition provided in the specification, a claim term is afforded its common definition in the art. Appellants submit the common definition of the term "to a living environment of the mammal," is understood to refer to the environment external to the mammal -- that is, the mammal's external living surroundings. Clearly, direct intraperitoneal injection does not constitute administration to the living environment of the mammal. Similarly, both the intratracheal administration taught by Khan and the intranasal administration taught by Baldridge are accomplished by restraining an animal and administering a solution inside the animal - either inside the nose, or inside the trachea. Appellants submit this invasive mode of administration is not the same as, nor encompassed by the term "application to the living environment of the mammal." In fact, none of the applied references teach or suggest the administration of IR-LPS to the external surroundings, or living environment, of the mammal. In every instance, the animals treated by Khan, Previte, and Baldridge were restrained and/or sedated so that a solution could be placed directly inside the animal. Hence, Appellants submit the combination of Khan, Previte, and Baldridge fails to teach or suggest the limitation "to a living environment of the mammal."

Further, all claim limitations must be considered in an obviousness rejection. 35 U.S.C. § 103 provides that:

> A patent may not be obtained.., if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

(Emphasis added). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Appellants submit that Khan explicitly teaches away from the use of LPS in reducing subsequent allergic responses, and since Khan states that "airway exposure to LPS produces transient AHR (airway hyperresponsiveness) and inflammation in developing mice and does not appear to influence functional and immune responses induced by subsequent allergen sensitization" (Khan, last paragraph, emphasis added). The Examiner contends that Khan "is

being relied upon for its specific teachings, namely the administration of LPS to neonatal or immature mammals to decrease development of allergic asthma." However, the Examiner's application of Khan completely disregards the ultimate conclusion of Khan, which is that LPS produces only transient airway hyperresponsiveness and does not appear to influence later functional and immune responses to allergic challenge. Indeed, Khan expressly teaches that LPS does not appear to influence the very responses sought to be elicited by the present invention. Accordingly, Appellants submit Khan in fact teaches away from the present inventive methods.

Since Khan, Previte, and Baldridge together completely fail to address all claim limitations, Appellants assert the combined references fail to render obvious the subject matter as a whole. Absent any teaching or suggestion of the missing claim elements, Appellants submit the Examiner has failed to establish a prima facie case of obviousness under 35 U.S.C. § 103."

"Khan, Previte and Baldridge do not enable the instant inventive methods since the combination of references does not place the claimed invention in the possession of the public.

To render a later invention unpatentable for obviousness, the prior art must enable a person of ordinary skill in the art to make and use the later invention. The prior art must place the claimed invention in the possession of the public. Beckman Instruments, Inc. v. LKB Produktor LB, 892 F.2d 1547, 1551 (Fed. Cir. 1989). Appellants submit the combination of Khan, Previte and Baldridge does not enable the instant invention, since all claim elements are not taught or suggested by the references and one of ordinary skill in the art could not derive the claimed methods from the cited references without undue experimentation.

Even if the combination of Khan, Previte and Baldridge were proper (which Appellants contend it is not, in detail above), the combination itself still fails to enable the instant inventive methods. Combining the IR-LPS of Previte with the protocol of Khan and the weekly administration of Baldridge still enables, at best, nothing more than invasive intranasal, intratracheal, or intraperitoneal administration of a solution comprising IR-LPS. Appellants note that the ultimate findings of Khan teach only that "airway exposure to LPS produces transient AHR (airway hyperresponsiveness)and inflammation in developing mice" and, importantly, "does not appear to influence functional and immune responses induced by subsequent allergen sensitization (Khan, last paragraph, emphasis added). Appellants' methods, however, require administration of IR-LPS to the living environment of the mammal through repeated treatments during the maturation of the mammal in order to decrease development of allergic asthma.

Deriving the instant methods from a reading of Khan, Previte and Baldridge requires altering the mode of administration, which would require undue experimentation on the part of the ordinary skilled artisan to achieve, as well as conjuring an expectation of success despite Khan's teaching away from such expectation. That is, a practitioner would need to first conceive of the idea of administering IR-LPS to the external living environment of the mammal, rather than direct intratracheal (Khan), intranasal (Baldridge) or intraperitoneal (Previte) administration to the mammal itself, without any guidance or direction whatsoever in the cited references. Then,

the practitioner would need to experiment with different dosing regimens - varying from the single doses described in both Khan and Previte - in order to determine the present inventive method of decreasing development of allergic asthma in the mammal. Given the unpredictability in the art, the absence of direction in Khan and Previte, Khan's express teaching away, and the quantity of experimentation needed relative to the references, Appellants contend such a leap would necessarily require undue experimentation on the part of the ordinary skilled artisan. Since Khan, Previte and Baldridge together fail to place the present invention in the possession of the public, Appellants submit the instant inventive methods are not enabled by Khan, Previte and Baldridge."

"Secondary evidence of nonobviousness demonstrates the unexpectedly superior results of IR-LPS relative to LPS in the methods of the instant invention.

Even if a prima facie case of obviousness under §103 were established, Appellants' secondary evidence of nonobviousness rebuts the case. The Declaration of Dr. Sandor Sipka, M.D., Ph.D., executed February 23, 2009, filed March 2, 2009 ("The March 2009 Declaration"), included herewith in the Evidence Appendix, demonstrates unexpected results and must be afforded due consideration.

i.) The evidence should be afforded substantial weight because a nexus exists between the claimed invention and the evidence of unexpected results provided in the March 2009 Declaration.

In the March 2009 Declaration, Dr. Sipka described experimental protocols and results relating to comparing the in vivo immunomodulatory effects of IR-LPS versus LPS when administered in accordance with the instant invention (as a mist sprayed into the environment). As stated by Dr. Sipka, the results clearly demonstrate that "prolonged pretreatment of the environment of infant mice with IR-LPS acts to prevent the intensity of ragweed specific allergic reaction differentially when compared to native LPS" (page 3, paragraph 6).

The Examiner has asserted that the Declaration does not provide evidence of an unpredicted differential impact of IR-LPS over LPS. The Examiner merely dismissed the data set forth in the Declaration as "neither surprising nor ... commensurate in scope with the claims, which are directed to a method of decreasing development of allergic asthma in neonatal or immature mammals by administration to a living environment of the mammal at least weekly."

To be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the subject matter as claimed. The examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations. Ashland Oil, Inc. v. Delta Resins & Refractories,

Inc., 776 F.2d 281,305, 227 USPQ 657, 673-674 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). The term "nexus" designates a factually and legally sufficient connection between the objective evidence of nonobviousness and the claimed invention so that the evidence is of probative value in the determination of nonobviousness. Demaco Corp. v. F. Von Langsdorff LicensingLtd, 851 F.2d 1387, 7 U.S.P.Q.2d 1222 (Fed. Cir.), cert. denied, 488 U.S. 956 (1988).

Appellants submit the March 2009 Declaration is most certainly relevant to the instantly claimed methods. The experimental method reported in the March 2009 Declaration aligns with the present claims, including (1) exposing immature mammals (6 week mice at beginning of treatment) to either IR-LPS or LPS (2) on an at least weekly basis (daily for eight weeks, during the maturation period of the mammal) (3) to the living environment of the mammal (misting the cages). In order to assess the effects on development of allergic disease, animals were then sensitized with ragweed allergen and later challenged with the allergen. Macrophage and neutrophil counts were determined for bronchial lavage samples (BAL), as well as cytokine concentrations for TNF-~ (a TH 1 cytokine), IL-4, and IL-5 (a Th 2 cytokine). (See March 2009 Declaration, page 2, paragraph 4). The effect on allergic disease development was evaluated by assessing these indicators of allergic disease -- macrophage and neutrophil numbers, as well as in vivo immunomodulatory effects on cytokines, particularly the TH 1 cytokine, TNF-a.

Clearly, a nexus exists between the claimed invention, which provides methods for decreasing allergic asthma, and the data, which demonstrate the comparative unexpected superiority of IR-LPS in protecting against allergic disease, as evidenced by analysis of macrophage and neutrophil numbers as well as TNF-α levels. That is, a legally .and factually sufficient connection between the claimed invention and the objective evidence of nonobviousness is present, such that the evidence should be considered in the determination of nonobviousness. Given the nexus between Dr. Sipka's data and the instant claimed invention, Appellants submit the Examiner erred in failing to consider and afford proper weight to the factual evidence provided by Dr. Sipka in the March 2009 Declaration.

ii). The surprisingly superior effect of IR-LPS over native LPS provides evidence of unexpected results that rebuts any prima facie case of obviousness.

Appellants submit the results reported in the March 2009 Declaration provide evidence of the surprising superiority of IR-LPS compared to native LPS, with respect to stimulating the TH 1 arm of the immune system and protecting against hyper-immune response to an allergen. According to Dr. Sipka, the results illustrate "a striking difference between the in vivo immunomodulatory effects of IR-LPS and native LPS on macrophage and neutrophil numbers," (March 2009 Declaration, page 3, paragraph 6). Further, TNF-a levels were increased significantly by 3.56 fold compared to controls for the IR-LPS, as compared with 1.66 fold for native LPS (see March 2009 Declaration, page 3, paragraph 6). Dr. Sipka specifically stated the results indicate a "surprisingly superior effect of IR-LPS over LPS in protecting against the

development of hyper-immune response to an allergen neither taught nor suggested by any of the prior art" cited by the Examiner or known to him (March 2009 Declaration, page 4, paragraph 7).

Neither Khan nor Previte teach or suggest the superior effects of IR-LPS compared to native LPS in protecting against the development of allergic disease. Accordingly, Appellants submit the March 2009 Declaration provided by Dr. Sipka constitutes secondary evidence of nonobviousness rebutting any prima facie case of obviousness, since it clearly demonstrates that, specifically with respect to the methods of the instant invention, IR-LPS yields unexpectedly superior results in decreasing allergic response, relative to native LPS.

For the reasons set forth above, Appellants respectfully request that the Board reverse the final rejection of claims 1-3, 5, 10, 17-18, and 22-25 as being obvious under 35 U.S.C. §103 over Khan in view of Previte and Baldridge."

It is the Examiner's position that Appellants argument that submit Khan explicitly teaches away from the use of LPS in reducing subsequent allergic responses since Khan states that "airway exposure to LPS produces transient AHR (airway hyperresponsiveness) and inflammation in developing mice and does not appear to influence functional and immune responses induced by subsequent allergen sensitization" is unpersuasive. The lack of complete prevention or treatment of hyperresponsiveness does not "teach away" from the instant invention. Furthermore, a careful reading of the reference shows that exposure to LPS did not significantly affect allergen-induced AHR, eosinophilic inflammation and cytokine production. The transient AHR cited by Applicant has nothing to do with allergic asthma or its prevention as the AHR occurred prior to allergen sensitization and challenge (In particular, 'Results'). The reference teaches that it "does not appear to influence the functional and immune responses induced by allergen sensitization." However, the reference does not teach away, particularly since the same reference teaches that "recent evidence has suggested that post-natal exposure to endotoxin may protect against the development of allergen sensitization and asthma." The

Examiner relies on the Khan reference for its motivation and specific teachings, namely the administration of LPS to neonatal or immature mammals to decrease development of allergic asthma.

It is the Examiner's position that one of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in the process for decreasing allergic asthma of Khan et al. because the process should be safe and without toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Therefore, it is obvious to use a safer, less toxic form of LPS in neonatal or immature mammals to decrease allergic asthma. Baldridge et al. teaches that at least weekly administration of LPS-derived MPL results in a protective Th1 response, so it would be obvious to perform the method of Khan and Previte at least weekly to attain a protective Th1 response to decrease allergic asthma.

Applicant's assertion that the common definition of the term "to a living environment of the mammal," is understood to refer to the "environment external to the mammal" or "the mammal's external living surroundings" is not supported by facts. The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01 In addition, even as defined above by Applicant, saline and air are both encompassed by these definitions. Saline and air are external to the mammal and in their living environment prior to administration intraperitoneally and intranasally. Applicant's argument about the invasiveness and restraint of the method of administration playing a role in whether or not application is from a living environment is not persuasive. Applicant intends for

this invention to encompass diapers and wipes, which undeniably involve restraint and invasiveness in their application.

The dosing schedule is an art-recognized results-effective variable which is well within the purview of those of ordinary skill in the art at the time the invention was made. Therefore, the recited at least weekly dosing schedule lends no patentable import to the claimed invention. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). See MPEP § 2144.05 part II. Applicants have not provided evidence of the criticality of the claimed dosing schedule, nor have they shown that the claimed dosing schedule produces unexpected results. The Examiner has additionally provided the Baldridge et al. reference to make the record clear that one of ordinary skill in the art would administer LPS-derived compounds at least weekly and that the resulting immune response would be the Th1 response that is necessary to establish a protective effect in the treatment of allergic asthma.

Applicant's arguments that the MPL of Baldridge et al. and LPS differ in structure and that MPL was only given in Baldridge et al. as an adjuvant are unpersuasive. The effect of the LPS and LPS derived MPL molecule is the same: to drive a Th1 response in the presence of other antigens to skew the response that is generated to the antigen. Therefore, the instant method and Baldridge references are directed to the same mechanism of action. Baldridge demonstrates that more than once weekly administration of LPS-derived MPL induces a Th1 response, as expected.

Applicant's argument that the Previte reference teaches away from the claimed invention is unpersuasive. It is the Examiner's position that Previte teaches that lethality is decreased in general and that is all that is required of the reference to make the argument that when giving LPS to children irradiated LPS would be preferred since it exhibits decreased lethality over non-irradiated LPS. Applicant's assertions that lethality is still higher than what would be considered acceptable in a treatment and that Previte teaches an unacceptable degree of toxicity for medical uses is unpersuasive. For purposes of the instant rejection what is or is not an acceptable degree of toxicity is not for Applicant to decide, nor is it a matter of what standards are presently medically acceptable for humans in the United States. The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01 The reference teaches that toxicity is decreased and that teaching alone provides motivation to use irradiated LPS in place of LPS. It is noted that LPS is fully toxic and is being used medically in both the Previte et al. and Khan et al. references.

The facts that Previte administers IR-LPS intraperitoneally to adult subjects and not to neonates and does not teach the use of IR-LPS to treat asthma does not preclude the use of the reference in the instant rejection. The Previte reference is relied on for its teaching that irradiated LPS is less toxic than non-irradiated LPS.

It is the Examiner's position that if the instant claims are enabled, so is the prior art. If irradiated LPS stimulates the Th1 arm of the animal's immune system in accordance with the present methods, then it would function in the same manner in the prior art. The motivation to use irradiated LPS over LPS has to do with decreased toxicity. The stimulation of the Th1 arm of the animal's immune system is inherent in using the irradiated LPS. Therefore, it remains the

Examiner's position that the combination of the references does indeed place the claimed invention in possession of the public.

A showing of unexpected results must be based on evidence, not argument or speculation. In re Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997) (conclusory statements that claimed compound possesses unusually low immune response or unexpected biological activity that is unsupported by comparative data held insufficient to overcome prima facie case of obviousness). The declaration by Sandor Sipka filed on 03/02/2009 provides evidence of the effect of irradiated vs. non-irradiated LPS given daily in aerosol form for 8 weeks on the development of macrophages and neutrophils in bronchial lavage and the production of TNF-α and IL-5 in serum of young mice sensitized peritoneally with ragweed antigen after challenge with ragweed antigen (presumably also peritoneally, but the declaration is silent as to the route of challenge administration). It is noted that models of allergic asthma generally use a respiratory challenge, not a peritoneal challenge.

The results set forth in the 03/02/2009 declaration by Sandor Sipka do not provide evidence of decreased development of allergic asthma. It is argument and speculation to say that that measuring macrophages, neutrophils, TNF-α and IL-5 in the mice is evidence of unexpectedly decreased development of allergic asthma. Allergic asthma is characterized by airway hyperresponsiveness, eosinophilic lung inflammation, mucus hypersecretion and elevated IgE. Applicants have not met their burden of establishing that allergic asthma was decreased at all in the IR-LPS treated animals, much less decreased unexpectedly.

The results set forth in the declaration, specifically Tables I and II are not surprising or unexpected. First, there is no evidence of record indicating that a protective effect is generated by decreased macrophages and neutrophils, as there is no evidence to suggest that increased macrophages and neutrophils are associated with allergic asthma. Further, p values of .04 and .02, respectively, are not evidence of surprising results. Further, there is no evidence of record to show that increased TNF-α and IL-5 are associated with a protective effect. The significant difference in TNF-α with a p value of .0001 is not evidence of a surprising result because there is no establishment on the record the increased TNF-α is independently protective against the development of allergic asthma. In the same way, the data showing that IL-5 is undetectable in LPS and control, but detectable in IR-LPS does not establish surprising results. The data taken together shows that irradiated LPS is not surprisingly better than non-irradiated LPS, even in the specific variables measured. It is noted that LPS has been shown in the literature to provide a protective effect, so the data should demonstrate that already established protective effect as well as the surprisingly protective effect of IR-LPS over LPS. It is noted that evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant,

practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991.

Even if Applicants had met their burden to establish unexpected results, the results are not commensurate in scope with the claims. The results do not demonstrate decreased development of allergic asthma in a neonatal or immature mammal by exposure with irradiation-detoxified LPS to a living environment. The claims encompass: 1.) asthma induced by any allergen, including allergens completely different from ragweed or pollen, such as cat and dust mite allergens; 2.) decreasing allergic asthma in all mammals, including humans; and 3.) exposing the mammal to IR-LPS by way of anything in their living environment. It remains the Examiner's position that the Declaration of Sandor Sipka is not sufficient to establish unexpected results for the exact experiments set forth in the declaration, much less for the full scope of the claims.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Nora M Rooney/
Primary Examiner, Art Unit 1644
December 17, 2010

Conferees:

/Ram R. Shukla/

Supervisory Patent Examiner, Art Unit 1644

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649